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Results after simultaneous surgery and RFA liver ablation for patients with colorectal carcinoma and synchronous liver metastases

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ABSTRACT

Background: Approximately 20% of patients with colorectal cancer present with synchronous liver metastases (sCRLM). These patients can be treated with a "one-step procedure" or staged resection, with or without radiofrequency ablation (RFA). Colorectal surgery in combination with intraoperative RFA leads to concerns regarding postoperative complications and survival. The purpose was to evaluate the one-step procedure with or without RFA in patients with sCRLM.

Materials and methods: Between January 2000 and September 2018, patients with sCRLM were selected in two tertiary referral centers and retrospectively analyzed. Postoperative morbidity and survival were analyzed.

Results: From a total of 410 patients presenting with sCRLM, 329 patients underwent a staged resection and 81 a one-step procedure. The 3-year overall survival (OS) was respectively 66% and 69% for one-step procedure and staged resection ($P = 0.24$). A total of 18 patients underwent RFA during the one step procedure. No significant differences were shown in postoperative complications whether intraoperative RFA was used in patients with sCRLM. In the one-step procedure, the 3-year OS was respectively 43% and 72% wheter patients did or did not receive RFA ($P = 0.19$).

Conclusion: OS for patients with sCRLM was similar for both one-step procedure and staged resection. Intraoperative RFA for sCRLM is technically safe.

Introduction

Synchronous liver metastases are present in approximately 20% of patients with colorectal cancer, of which the majority present with liver-only metastases [1]. Treatment for most patients consists of palliative chemotherapy. An increasing number of patients with synchronous colorectal liver metastases (sCRLM) qualify for treatment of both their primary and metastatic disease with a curative intent [2–4].

In patients with synchronous disease, i.e. simultaneous existence of both primary and secondary tumors, uncertainty exists whether to treat in a staged approach or to treat all sites in one session [5,6]. Arguments for this latter "one-step procedure" are unnecessity of a second surgical intervention, shorter cumulative hospital stay, lower complication rate and lower cumulative costs [7–9]. Arguments for a staged approach are synchronous metastases originating from locally advanced rectal cancer requiring chemoradiotherapy and extensive bilobar liver metastases that can not be addressed in one surgical procedure [10]. Patients are only eligible for partial hepatectomy in about 10–15% of cases [11]. This is due to, for instance, a lack of sufficient remnant liver parenchyma, close proximity to large vessels, a location requiring a disproportionate loss of normal liver tissue or the presence of extrahepatic disease. In order to overcome these limitations,

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several additional multimodality treatments have become available, such as induction chemotherapy for downstaging, portal vein embolization and ablative techniques, of which radiofrequency ablation (RFA) is frequently used [12–17].

Although percutaneous RFA is considered a minimally invasive technique, it is still associated with possible severe complications such as posttreatment hemorraghes, intestinal perforation and liver abscesses [18,19]. The combination of intra-operative RFA and resection of liver metastases in one setting has already been shown to be a safe combination [20]. However, in the setting of simultaneous resection for the primary colorectal cancer and liver metastases, the addition of RFA to the liver resection may hypothetically still lead to an increase in intra-abdominal abscesses near the liver, since the necrotic area created by the thermal ablation might easily be contaminated during the procedure.

Patients with synchronous disease are increasingly treated with a combination of ablation and surgery. To our knowledge only a small number of studies have reported on the specific setting where a combination of surgery and RFA is used for patients where resection of primary colorectal tumor and liver metastates is performed in one procedure [21–23]. This study aims to provide insight in outcome regarding simultaneous resection and staged resection of synchronous disease with additional evaluations on intra-operative RFA in patients who undergo resection of the primary tumor and liver metastases.

Materials and methods

Patients

Patients with sCRLM, were included in a prospective multicenter database of two tertiary referral hospitals (Erasmus MC Cancer Institute, Rotterdam, The Netherlands; Radboudumc, Nijmegen, The Netherlands). Data concerning patient demographics, primary tumor staging, treatment characteristics, post-operative characteristics and follow-up were retrospectively analyzed.

The database consisted of 1166 patients who were surgically treated for colorectal liver metastases between January 2000 and September 2018. A total of 611 patients presented with synchronous liver metastases, defined as presenting with CLRM at the time of detection of the primary tumor. After exclusion of patients with extrahepatic disease (n = 65), lack of follow-up data or missing data (n = 89) and the use of a two staged liver approach (n = 59), in which 12 patients showed multiple exclusion criteria, a total of 410 patients were available for analysis. Only patients who were curatively treated were analyzed, i.e., patients with progression during a staged approach, deeming them unresectable, were excluded (Fig. 1).

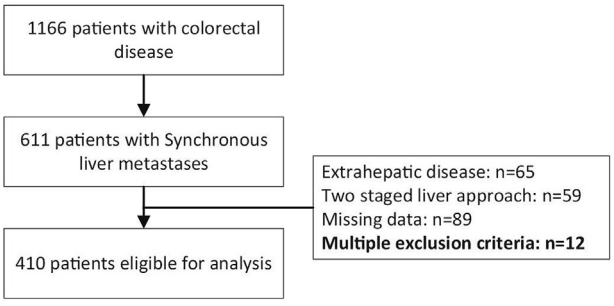


Fig. 1. Flow diagram patients in database.

All treated patients received standard evaluation with medical history, physical examination and serum laboratory tests. The laboratory tests consisted of ABO typing, blood count, coagulation profile, electrolytes, renal panel, liver function values, proteins and glucose. Patients also received standard imaging such as thoracoabdominal contrast enhanced computed tomography (CT) and/or combined CT and full body positron emission tomography (PET-CT) for further evaluation. All patients were discussed, prior to treatment, in multidisciplinary tumor boards. Neoadjuvant chemotherapy is not considered standard patient care in our hospitals if radical resection is deemed possible, a future liver remnant of 20–30% is expected and the vascular and biliary system of the remaining segments can be preserved. If this was considered not feasible, for example due to ill location or due to multiple metastases, patients received induction chemotherapy. Due to the tertiary nature of our hospitals, some patients already received neoadjuvant/induction chemotherapy according to the treatment protocols of referring hospitals.

Induction chemotherapy, in these patients, consisted of 5-fluorouracil/capecitabine with irinotecan or oxaliplatin together with or without bevacizumab. After 2 to 3 cycles, response was assessed using contrast enhanced CT (CE-CT) and CEA serum levels. Depending on this response, further surgical treatment was considered. Surgery was usually planned 3–4 weeks after the last dose of chemotherapy with an additional interval of at least 6 weeks after the last course of bevacizumab. Adjuvant chemotherapy was given in only a minority of patients (14.8%) as part of a study protocol in the Netherlands [24].

Surgery

Patients underwent surgical resection of both the primary and CRLM in case of an easily resectable colorectal primary and usually a minor hepatectomy. Staged resections were patients who either underwent resection of the primary in a referral hospital or were considered too extensive for resection in a one-step procedure. In case the lesions in the liver were considered unresectable during planning or due to additional intraoperative findings such as ill location of metastases or lack of remnant/remaining liver parenchyma, RFA was considered. During the procedure, intraoperative ultrasound and inspection of the abdominal cavity was performed to verify the absence of extrahepatic metastases and the localization of tumors in the liver. For the treatment of the liver metastases, the size, location and relation to the vasculature was used to determine the extent of the resection. The Cavitron Ultrasonic Surgical Aspirator (CUSA) was used for the liver surgery. The colorectal surgery was performed according to the accepted principles for open surgery. All resected specimens were reviewed by an experienced pathologist; R1 resection was defined as the presence of tumor invasion in the resection margin, while R0 was defined as the lack of tumor invasion [25].

Radiofrequency ablation

In case of liver metastases, up to 3 cm in diameter, that could not be surgically resected, RFA was added to the therapy. RFA was mainly performed in patients in which the future liver remnant was expected to be too small, e.g. due to ill positioned lesions providing a disproportionate loss of liver parenchyma after surgery, or due to multifocality of disease. An RFA-needle (Cool-Tip™, Covidien, Boulder, CO, USA; Jet-Tip™, RF Medical Co., Campagnola di Zevio, Italia) was placed in the tumor under ultrasound guidance, after which electromagnetic waves (375–500 kHz) were introduced, resulting in coagulation. Depending on the size of the lesion, different types of needles were used. Adequate positioning and

technical success were considered for complete ablation.

Follow-up

The data was finalized in 2018, with a median follow-up of 28 months (0–145 months). After treatment, different complications were categorized according to the Clavien-Dindo classification [26]. 90-day mortality was graded as Clavien-Dindo grade V. Complications were indexed and separately analyzed. Special attention was given towards intra-abdominal abscess near the liver and total amount of postoperative infections. Further follow-up consisted of clinical evaluation and serum tests every 3 months. The two participating centers had a slight deviation in follow-up protocol. In one center patients received imaging (ultrasound or contrast-enhanced chest/abdominal CT) every 4 months for the first year and every 6 months in the second year and thereafter yearly. In the other hospital, follow-up consisted of additional imaging every 3 months for the first 3 years and every 6 months in the two years after. In case of a recurrence, the tumor board made a decision concerning further treatment. The time between surgery and recurrence of disease inside or outside the liver was used to define disease-free survival (DFS). Overall survival (OS) was defined as the period between the procedure and the end of follow-up. Post-operative results such as complications, mortality, DFS and OS were analyzed.

Statistical analysis

Statistical analysis was performed by using SPSS (IBM SPSS Statistics for Windows, version 20, SPSS, Chicago, Ill). The Mann-Whitney *U* test was used for continuous data, while the Chi-square test was used for categorical data. Survival was analyzed with the use of the Kaplan-Meier test for both DFS and OS. Differences in survival were analyzed with the log rank test. Multivariate analysis could not be performed, due to the small patient population. A P-value of 0.05 and lower was considered significant.

Results

Patients

Of the total group of 410 patients treated for sCRLM, 81 patients (20%) received a one-step procedure of the primary tumor and liver metastases, 329 patients (80%) received staged resections. Of the patients who were treated with the one-step procedure, 18 patients also underwent intraoperative RFA ablation (22%) and 63 patients were treated with resection only (78%). Neoadjuvant chemotherapy was given in 234 of the 410 patients (57%). When evaluated according to treatment from 2000 to 2009 and 2010–2018, no significant difference in the number of patients receiving neoadjuvant treatment was observed (respectively 59% and 56%; P = 0.63).

Median follow-up of patients after the staged resection was 29 months (IQR 0–62 months) and 25 months (IQR 0–54 months) after the one-step procedure. Baseline characteristics differed slightly between patients treated in the one-step procedure versus patients treated in a staged strategy. Patients undergoing a staged approach had a larger median size of the largest liver metastasis (P = 0.05), and neadjuvant chemotherapy was administerd more often (P = 0.001; Table 1A). Patients who underwent a one-step procedure for sCRLM showed a larger number of metastases if they were treated with additional RFA in the session compared to those without additional RFA (P = 0.001; Table 1B).

Complications

Postoperative complications could not accurately be assessed for patients with a one-step procedure compared to the staged resection because the patients included in the participating hospitals were tertiary referral centers and the resection of the primary tumor in the staged resection was performed in other hospitals, resulting in loss of information. For this reason postoperative results were not analyzed between staged resection and the patients who received one-step procedure. The use of neoadjuvant chemotherapy for further downstaging in all the patients with synchronous metastases did not lead to significant differences in postoperative complications (P = 0.93).

Patients who received additional RFA during the one-step procedure had significantly shorter hospital stay compared to the patients without RFA (P = 0.04). No significant differences were shown in post-operative complications between the two groups (Table 2).

Disease-free survival

The 3-year DFS for the one-step procedure was 12% compared to a 3-year DFS of 31% for patients treated with a staged approach, median survival was 9 (IQR 6–11) and 13 months (IQR 11–15) respectively (Fig. 2; P = 0.001). The 3-year DFS for patients with

Table 1A
Patient characteristics for patients with sCRLM receiving one-step procedure or Staged resection.

Characteristics		one-step procedure (n = 81)	Staged resection (n = 329)	P-value
Age at surgery (mean [95% CI])		65 years (63–67)	63 years (62–64)	0.29
Gender (M:F)		49:32 (61% male)	208:121 (63% male)	0.65
Comorbidities		33 patients (41%)	145 patients (46%)	0.45
ASA classification	Class I	25 (31%)	86 (27%)	0.75
	Class II	33 (41%)	141 (44%)	
	Class III	22 (27%)	82 (26%)	
	Class IV	1 (1%)	9 (3%)	
BMI (mean [95% CI])		25.8 kg/m^2 (24.8–26.8)	25.7 kg/m^2 (25.3–26.1)	0.42
Location Primary Tumor (Colon:Rectum)		55:26 (68% colon)	198:130 (60%)	0.22
T-stage primary	1	1 (1%)	5 (2%)	0.48
	2	8 (10%)	28 (9%)	
	3	51 (63%)	226 (72%)	
	4	18 (22%)	42 (13%)	
Positive lymph nodes		57 patients (71%)	205 patients (65%)	0.28
High risk Fong CRS (risk score 3–5)		41 patients (53%)	176 patients (56%)	0.62
Tumor Size (mean [95% CI])		3.1 cm (2.5–3.6 cm)	3.4 cm (3.1–3.6 cm)	0.05
Tumor Number (median [range])		2 metastases (1–14)	2 metastases (1–11)	0.41
Neoadjuvant chemotherapy		36 patients (44%)	198 patients (60%)	0.01
Adjuvant chemotherapy		14 patients (18%)	44 patients (14%)	0.45

Table 1B
Patient characteristics for patients with a one-step procedure with or without additional RFA.

Characteristics		With RFA (n = 18)	Without RFA (n = 63)	P-value
Age at surgery (mean [95% CI])		64 years (59–69)	65 years (63–68)	0.57
Gender (M:F)		9:9 (50% male)	40:23 (64% male)	0.30
Comorbidities		5 patients (28%)	28 patients (44%)	0.20
ASA classification	Class I	7 (39%)	18 (29%)	0.80
	Class II	7 (39%)	26 (41%)	
	Class III	4 (22%)	18 (29%)	
	Class IV	0 (0%)	1 (2%)	
BMI (mean [95% CI])		25.2 kg/m^2 (23.3–27.1)	26.0 kg/m^2 (24.8–27.2)	0.64
Location Primary Tumor (Colon:Rectum)		14:4 (78% colon)	41:22 (65% colon)	0.56
T-stage primary	1	0 (0%)	1 (2%)	0.55
	2	1 (6%)	7 (11%)	
	3	14 (78%)	37 (59%)	
	4	2 (11%)	16 (25%)	
Positive lymph nodes		13 patients (72%)	44 patients (71%)	0.92
High risk Fong CRS (risk score 3–5)		11 patients (69%)	30 patients (48%)	0.15
Tumor Size (mean [95% CI])		2.7 cm (1.8–3.6)	3.2 cm (2.5–3.8)	0.95
Tumor Number (median [range])		3 metastases (2–14)	1 metastases (1–13)	0.001
Neoadjuvant chemotherapy		11 patients (61%)	25 patients (40%)	0.11
Adjuvant chemotherapy		1 patient (6%)	13 patients (21%)	0.13

Table 2
Postoperative Results for patients with a one-step procedure with or without additional RFA.

Postoperative Results		With RFA (n = 18)	Without RFA (n = 63)	P-value
Major Resection (≥3 segments)		1 patient (6%)	10 patients (16%)	0.26
Complications		7 (39%)	40 (64%)	0.06
Clavien-Dindo Classification	Grade I	0 (0%)	8 (13%)	0.30
	Grade II	4 (22%)	11 (18%)	
	Grade III	2 (11%)	14 (22%)	
	Grade IV	1 (6%)	5 (8%)	
	Grade V	0 (0%)	2 (3%)	
Invasive: non-invasive complications		3 invasive (17%)	21 invasive (33%)	0.17
Transfusion necessity		2 (13%)	16 (28%)	0.20
Post-operative Infection		6 (33%)	23 (37%)	0.80
Pneumonia		1 (6%)	5 (8%)	0.73
Intra-abdominal abscess		2 (11%)	7 (11%)	1.00
Hospital stay (median [range])		9 days (5–27)	12 days (4–59)	0.04
Radicality (R0:R1)		15 R0 (83%)	56 R0 (89%)	0.53
Resection margin (median [range])		3 mm (0–14)	5 mm (0–20)	0.16

intraoperative RFA during the one-step procedure was 0% and without RFA 16%, median survival was respectively 4 (IQR 1–7) and 11 months (IQR 8–14)(Fig. 3; P = 0.001).

Overall survival

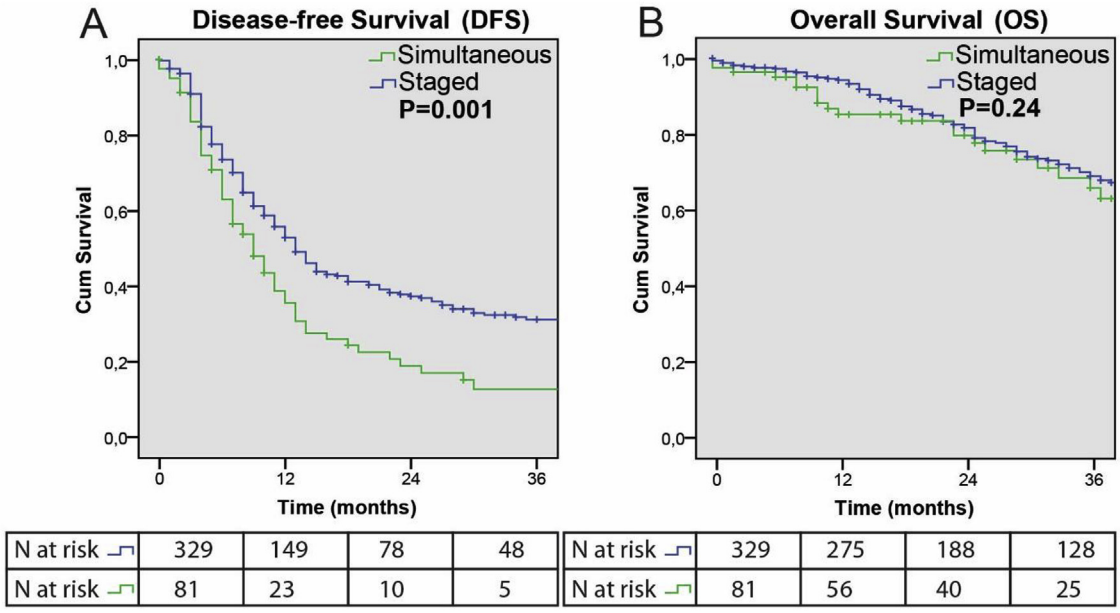
The 3-year OS between patients treated with the one-step procedure or staged operations was 66% and 69% with a median survival was 58 (IQR 36–80) and 71 months (IQR 52–90) respectively (Fig. 2; P = 0.24). The 3-year OS was 43% (median 36 months; IQR 17–55) if intraoperative RFA was performed during the one-step procedure and 72% (median 64 months; IQR 36–92) when the one-step procedure was performed without RFA (Fig. 3; P = 0.19).

Discussion

For the treatment of unresectable or borderline resectable colorectal liver metastases (CRLM) many treatment strategies have been developed. Both systemic (induction chemotherapy) and surgical strategies (e.g. portal vein embolization or a two staged procedure) are established options to convert patients to a resectable state. For patients who still remain ineligible for surgical resection, additional ablative treatments such as radiofrequency ablation (RFA) are frequently used to treat these patients with a curative intent [12–16]. The use of additional intraoperative RFA during treatment of patients with sCRLM is technically safe but is associated with lower 3-year DFS and OS.

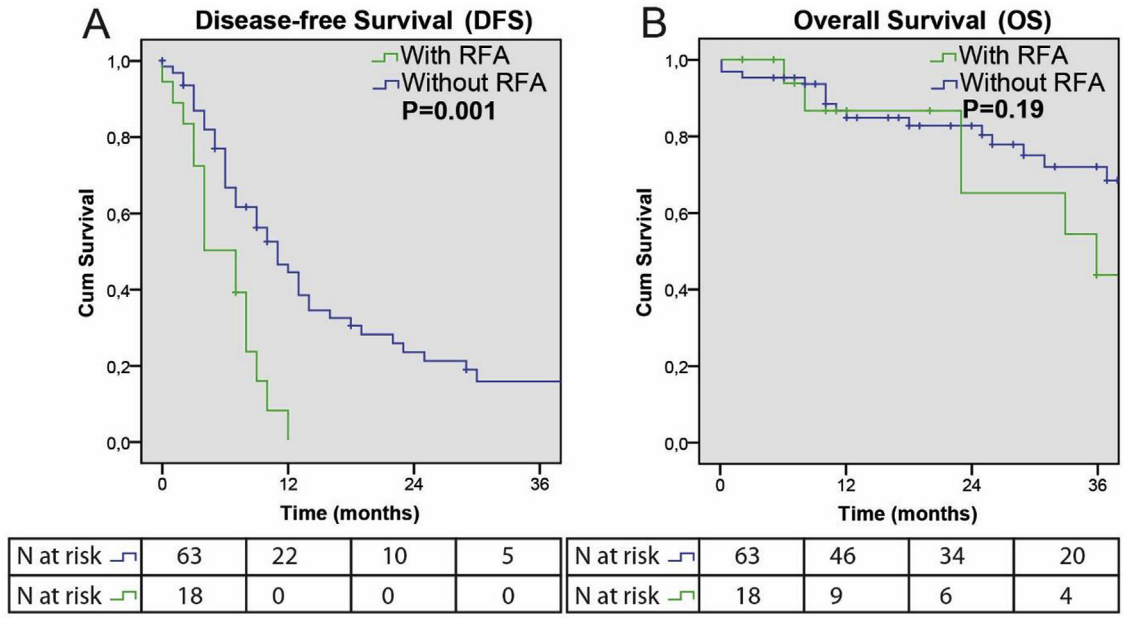
Several authors have demonstrated that a simultaneous approach for sCRLM results in similar results compared to staged approach for sCRLM [10,27,28]. However, in the current study, a simultaneous procedure showed lower DFS compared to a staged approach. Most likely this is because in case of a simultaneous resection, small lesions are not detectable yet whereas in a staged procedure there is a test of time, and small lesions become visible and resectable at the time of the successive procedure. These differences in DFS did not translate in superior OS for the staged approach. The primary colorectal resection during the staged resection was often performed in secondary hospitals. Therefore, postoperative complications after one-step procedure and staged resection was not evaluated.

Addition of intraoperative RFA in patients with sCRLM treated in a one-step procedure did not lead to any significant differences in postoperative complications, e.g., postoperative infections and 90-day mortality compared to patients treated with resection only. However, if RFA was performed during the one-step procedure, patients showed a lower 3-year DFS and OS compared to those treated without RF, possibly due to differences in patient characteristics. Patients treated with additional intraoperative RFA presented with a higher Fong CRS [29] and higher tumor load. This means these patients were only eligible for curative resection with the use of an additional ablation. Due to their worse clinical



N at risk	329	149	78	48	N at risk	329	275	188	128
N at risk	81	23	10	5	N at risk	81	56	40	25

Fig. 2. One-step procedure vs staged resections. A. Disease-free Survival (DFS) between one-step procedure and staged resections of the primary and secondary tumors. The 3-year DFS is respectively 12% and 31% (P = 0.001). B. Overall survival (OS) between one-step procedure and staged resections with a 3-year OS of respectively 66% and 69% (P = 0.24).



N at risk	63	22	10	5	N at risk	63	46	34	20
N at risk	18	0	0	0	N at risk	18	9	6	4

Fig. 3. RFA in sCRLM during the one-step procedure. A. Disease-free survival (DFS) for patients with sCRLM treated with RFA compared to patients treated without RFA during the one-step procedure. The 3-year DFS is respectively 0% and 16% (P = 0.001). B. Overall survival (OS) for these patients with a 3-year OS of respectively 43% and 72% (P = 0.19).

presentation a less favorable clinical outcome can be expected. We believe that not RFA by itself induces shorter DFS and recurrences, but that other factors (e.g. multiple, ill-located lesions) are the reason for these worse long term results [17].

A Dutch nationwide database study, recently demonstrated a median overall survival for synchronous disease with liver metastases only, to be approximately 46 months [2] and median DFS of approximately 10 months [21,30,31]. This is comparable to the median overall survival of studied patients with synchronous treatment in the current study. Most patients who receive additional treatment with RFA during surgery, however, would not have received curative treatment without the addition of an ablative technique. Median OS for patients without curative treatment, i.e., patients with only systemic chemotherapy or best supportive care was reported to be around 15 months and 3 months respectively [2]. This shows a clear survival benefit for patients who would otherwise have unresectable disease.

The current study has limitations, such as the small patient population and selection bias between patients who either received RFA and those who did not. Another limitation is the potential difference in local treatment protocols of the two participating hospitals, such as whether RFA should be included in the

treatment or not. This effect was considered small because every patient was discussed in a multi-disciplinary tumor board. Another drawback concerns the comparative analysis of OS between staged and simultaneously treated patients. These OS data are biased as patients with recurrent disease within the time interval between a two staged approach are excluded from OS analysis for not completing the staged strategy. Consequently, the analysis then overestimates OS in this patient group. Also, in this relatively small subgroups of patients, other known risk factors, such as location of the primary, size of the metastases or the use of (neo)adjuvant therapy could not be analyzed in this study.

In conclusion, overall survival is similar in patients with sCRLM treated with the one-step procedure compared to staged resection. The use of intraoperative RFA during treatment of patients with sCRLM is technically safe but is associated with lower DFS and OS. Patient selection plays a major role in the differences whether additional RFA was performed or not, implying that future prospective trials are required to accurately determine the effects of RFA in CRLM [11].

Disclosures

The authors declare no conflict of interest or any disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.016.

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